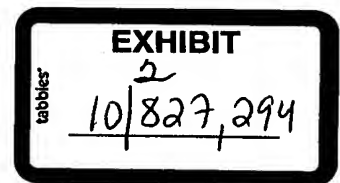


② Osteoarthritis



The role of cytokines in osteoarthritis pathophysiology

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Abstract. Morphological changes observed in OA include cartilage erosion as well as a variable degree of synovial inflammation. Current research attributes these changes to a complex network of biochemical factors, including proteolytic enzymes, that lead to a breakdown of the cartilage macromolecules. Cytokines such as IL-1 and TNF- α produced by activated synoviocytes, mononuclear cells or by articular cartilage itself significantly up-regulate metalloproteinases (MMP) gene expression. Cytokines also blunt chondrocyte compensatory synthesis pathways required to restore the integrity of the degraded extracellular matrix (ECM). Moreover, in OA synovium, a relative deficit in the production of natural antagonists of the IL-1 receptor (IL-1Ra) has been demonstrated, and could possibly be related to an excess production of nitric oxide in OA tissues. This, coupled with an upregulation in the receptor level, has been shown to be an additional enhancer of the catabolic effect of IL-1 in this disease.

IL-1 and TNF- α significantly up-regulate MMP-3 steady-state mRNA derived from human synovium and chondrocytes. The neutralization of IL-1 and/or TNF- α up-regulation of MMP gene expression appears to be a logical development in the potential medical therapy of OA. Indeed, recombinant IL-1receptor antagonists (ILRa) and soluble IL-1 receptor proteins have been tested in both animal models of OA for modification of OA progression. Soluble IL-1Ra suppressed MMP-3 transcription in the rabbit synovial cell line HIG-82. Experimental evidence showing that neutralizing TNF- α suppressed cartilage degradation in arthritis also support such strategy. The important role of TNF- α in OA may emerge from the fact that human articular chondrocytes from OA cartilage expressed a significantly higher number of the p55 TNF- α receptor which could make OA cartilage particularly susceptible to TNF- α degradative stimuli. In addition, OA cartilage produces more TNF- α and TNF- α convertase enzyme (TACE) mRNA than normal cartilage. By analogy, an inhibitor to the p55 TNF- α receptor may also provide a mechanism for abolishing TNF- α -induced degradation of cartilage ECM by MMPs. Since TACE is the regulator of TNF- α activity, limiting the activity of TACE might also prove efficacious in OA. IL-1 and TNF- α inhibition of chondrocyte compensatory biosynthesis pathways which further compromise cartilage repair must also be dealt with, perhaps by employing stimulatory agents such as transforming growth factor-beta or insulin-like growth factor-I.

Certain cytokines have antiinflammatory properties. Three such cytokines – IL-4, IL-10, and IL-13 – have been identified as able to modulate various inflammatory processes. Their antiinflammatory potential, however, appears to depend greatly on the target cell. Interleukin-4 (IL-4) has been tested *in vitro* in OA tissue and has been shown to suppress the synthesis of both TNF- α and IL-1 β in the same manner as low-dose dexamethasone. Naturally occurring antiinflammatory cytokines such as IL-10 inhibit the synthesis of IL-1 and TNF- α and can be potential targets for therapy in OA. Augmenting inhibitor production *in situ* by gene therapy or supplementing it by injecting the recombinant protein is an attractive therapeutic target, although an *in vivo* assay in OA is not available, and its applicability has yet to be proven. Similarly, IL-13 significantly inhibits lipopolysaccharide (LPS)-induced TNF- α production by mononuclear cells from peripheral blood, but not in cells from inflamed synovial fluid. IL-13 has important biological activities: inhibition of the production of a wide range of proinflammatory cytokines in monocytes/macrophages, B cells, natural killer cells and endothelial cells, while increasing IL-1Ra production. In OA synovial membranes treated with LPS, IL-13 inhibited the synthesis of IL-1 β , TNF- α and stromelysin, while increasing IL-1Ra production.

In summary, modulation of cytokines that control MMP gene up-regulation would appear to be fertile targets for drug development in the treatment of OA. Several studies illustrate the potential importance of modulating IL-1 activity as a means to reduce the progression of the structural changes in OA. In the experimental dog and rabbit models of OA, we have demonstrated that *in vivo* intraarticular injections of the IL-Ra gene can prevent the progression of structural changes in OA. Future directions in the research and treatment of osteoarthritis (OA) will be based on the emerging picture of pathophysiological events that modulate the initiation and progression of OA.

Keywords: OA, proinflammatory cytokines, antiinflammatory cytokines, cytokine antagonists

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1. Introduction

Osteoarthritis (OA) is believed to be a consequence of mechanical and biological events that destabilize the normal coupling of degradation and synthesis within articular joint tissues. In primary OA, no trauma or other predisposing factor is identified, and intrinsic alterations of the articular tissue, or response to normal cumulative stresses, are presumed responsible [43]. The disease process affects not only the articular cartilage, but also the entire joint structure including the subchondral bone, ligaments, capsule, synovial membrane and periarticular muscles. Morphological changes observed in OA include cartilage erosion as well as a variable degree of synovial inflammation. Current research attributes these changes to a complex network of biochemical factors, including proteolytic enzymes, which lead to a breakdown of the cartilage macromolecules. This disease process involves a disturbance in the normal balance of degradation and repair in articular cartilage, synovial membrane and subchondral bone [33, 37, 53, 62].

2. Cytokines and osteoarthritis

It is believed that cytokines and growth factors play an important role in the pathophysiology of OA. They are closely associated with functional alterations in synovium, cartilage and subchondral bone, and are produced both spontaneously and following stimulation by the joint tissue cells. Cytokines such as IL-1 and TNF-alpha produced by activated synoviocytes, mononuclear cells or by articular cartilage itself significantly up-regulate metalloproteinases (MMP) gene expression. Cytokines also blunt chondrocyte compensatory synthesis pathways required to restore the integrity of the degraded extracellular matrix (ECM). Moreover, in OA synovium, a relative deficit in the production of natural antagonists of the IL-1 receptor (IL-1Ra) has been demonstrated, and could possibly be related to an excess production of nitric oxide in OA tissues. This, coupled with an upregulation in the receptor level, has been shown to be an additional enhancer of the catabolic effect of IL-1 in this disease. In OA synovial membrane, the synovial lining cells are key inflammatory effectors. Once cartilage degradation has begun, the synovial membrane phagocytoses the breakdown products released into the synovial fluid. Consequently, the membrane becomes hypertrophic and hyperplastic. Several studies have reported inflammatory changes in the synovial membrane of patients with OA that, on occasion, were almost indistinguishable from those in patients with an inflammatory arthritis such as rheumatoid arthritis (RA) [33, 37, 53, 62].

2.1. Proinflammatory cytokines

Proinflammatory cytokines are believed to play a pivotal role in the initiation and development of this disease process [19, 68, 87]. IL-1 and TNF-alpha can induce joint articular cells, such as chondrocytes and synovial cells, to produce other cytokines such as IL-8, IL-6, as well as stimulate proteases and prostaglandin E₂ (PGE₂) production. IL-1beta and TNF-alpha have also been shown to increase osteoclastic bone resorption *in vitro* [12]. Blocking IL-1 activity with the IL-1 receptor antagonist (IL-1Ra) in synovial fibroblasts *in vitro* reduced IL-6 and IL-8 production, but not TNF-alpha [34]. Moreover, adding anti-TNF-alpha antibodies to synovial cells greatly reduced the production of other proinflammatory cytokines such as IL-1, GM-CSF, IL-6 [15].

IL-1beta is primarily synthesized as a 31 kilodalton (kD) precursor and released in the active form of 17.5 kD [61, 79]. In synovial membrane, synovial fluid and cartilage, IL-1beta has been found in the active form. *Ex vivo* OA synovial membrane secretes this cytokine [67]. Several serine proteases can process the

pro-IL-1 β to bioactive form [13]. In mammals only one protease, belonging to the cysteine-dependent protease family and named IL-1 β converting enzyme (ICE or Caspase-1), can specifically generate the mature 17.5 kD cytokine [13,51]. ICE is a pro-enzyme polypeptide of 45 kD [p45] located in the plasma membrane [91]. The biological activation of cells by IL-1 is mediated through association with two specific cell-surface receptors (IL-1R), named type I and type II [80]. Type I receptor binds IL-1 β more than IL-1 α and appears responsible for signal transduction [8,59,71]. Type II IL-1R has a greater affinity for IL-1 α than IL-1 β . The number of type I IL-1R is significantly increased in OA chondrocytes and synovial fibroblasts [59,71]. This appears to be responsible for the higher sensitivity of these cells to stimulation by IL-1 [59].

Both types of IL-1R can also be shed from the cell surface, and exist extracellularly in truncated forms; they are named IL-1 soluble receptors (IL-1sR). The shed receptor may function as a receptor antagonist because the ligand-binding region is preserved, thus enabling it to compete with the membrane-associated receptors of the target cells. Similarly, the shedding of surface receptors may decrease the responsiveness of target cells to the ligand. It is suggested that type II IL-1R serves as the main precursor for shed soluble receptors. The binding affinity of IL-1sR to both IL-1 isoforms and IL-1Ra differs. Type II IL-1sR binds IL-1 β more readily than IL-1Ra; in contrast, type I IL-1sR binds IL-1Ra with high affinity [8,29,82].

TNF- α appears to be an important mediator of matrix degradation and a pivotal cytokine in synovial membrane inflammation in OA, although being detected in OA articular tissue low levels. TNF- α is synthesized as a precursor protein comprising 76 amino acids. Proteolytic cleavage takes place at the cellular surface via a TNF- α converting enzyme named TACE [14]. This enzyme is also required for shedding the TNF receptors. An upregulation of TACE mRNA in human OA cartilage has recently been reported [7]. Human TNF- α is converted to the 157-residue (17 kD) secreted protein that oligomerizes to form trimers [3].

TNF- α binds to two specific receptors on the cell membrane [28,73,76]. These two TNF-R have molecular masses of 55 to 60 kD and 75 to 80 kD [54,72], and are named according to their molecular weight; TNF-R55 and TNF-R75. Their extracellular domains share 28% identity [17,45]. There is a complete absence of homology between the intracellular domains of the two TNF-R and any other known protein receptor [52,54,72,81]. In articular tissue cells, TNF-R55 seems to be the dominant receptor responsible for mediating TNF- α activity. In OA chondrocytes and synovial fibroblasts, enhanced expression of TNF-R55 has been reported [4,90]. Both receptor types appear to be actively involved in signal transduction [4,42,63,77,85]. Each receptor type has been shown to induce a specific subset of TNF- α activities [44,84]. TNF-R55 and TNF-R75 are linked to distinct intracellular second-messengers. TNF-R75 may regulate the rate of TNF- α association to TNF-R55 [83]. TNF-R75/TNF- α complex may exhibit enhanced and/or specific intracellular function. Heterogeneity in the TNF- α response may also be caused by different postreceptor signal transduction pathways [75]. It is not clear, however, whether TNF- α receptor trimerization is necessary for activation, or whether receptor dimerization is sufficient, or if receptor trimerization triggers other and/or additional intracellular pathways.

Proteolytic cleavage of the extracellular domain of each TNF-R produces two soluble receptors, TNF-sR55 and TNF-sR75. OA synovial fibroblasts and chondrocytes release a significantly elevated level of TNF-sR75 [4,16]. A higher ratio of TNF-sR75/TNF-sR55 is noted in the more severe cases of arthritis [21,22,70]. At low concentrations, TNF-sR seems to stabilize the trimeric structure of TNF- α , thereby increasing the half-life of bioactive TNF- α [2], while at high concentrations, TNF-sR reduce the bioactivity of TNF- α by competing for TNF binding with cell-associated receptors [40]. How-

ever, as the affinity of both TNF-sR is similar to that of the plasma membrane receptor, large amounts of these inhibitors are required to decrease TNF- α activity.

The balance between cytokine-driven anabolic and catabolic processes determines the integrity of articular joint tissue. Other proinflammatory cytokines such as IL-6, IL-8, LIF, IL-11, and IL-17 have been shown to be expressed in OA tissue, and have therefore been considered potential contributing factors in the pathogenesis of this disease.

IL-6 has been proposed as a contributor to the OA pathological process by: (1) increasing the number of inflammatory cells in synovial tissue [35]; (2) stimulating the proliferation of chondrocytes; and (3) inducing an amplification of the IL-1 effects on the increased synthesis of metalloproteases (MMP) and inhibiting proteoglycan production [64]. However, as IL-6 can induce the production of TIMP [55], and not MMP, it is believed that this cytokine is involved in the feedback mechanism that limits proteolytic damage.

Interleukin-8 is a potent chemotactic cytokine for polymorphonuclear neutrophils (PMN), stimulating their chemotaxis and generating reactive oxygen metabolites [93]. This chemokine is synthesized by a variety of cells including monocytes/macrophages, chondrocytes and fibroblasts [41,49,50,86]. IL-8 plays an important role in the acute inflammatory reaction. In synovial culture, TNF- α stimulates the production of IL-8 in a time- and dose-dependent manner [41]. In OA patients, IL-1 β , IL-6, TNF- α and IL-8 coexist in the synovial fluid. IL-8 enhances the release of IL-1 β , IL-6 and TNF- α [93]. The presence of IL-8 in the lining cell layers could explain the high amount of IL-8 in the synovial fluid [27]. IL-8 is also present in the chondrocytes, and has been shown to enhance the production of oxidative and 5-lipoxygenase products [74]. Stimulated human articular chondrocytes express the IL-8 gene and secrete bioactive IL-8 [57].

Leukemia inhibitory factor (LIF) is a single-chain glycoprotein that has diverse effects, including induction of acute-phase protein synthesis and the inhibition of lipoprotein lipase activity. LIF level has been detected in synovial fluid of OA patients [25]. LIF has been shown to enhance IL-1 β and IL-8 expression in chondrocytes, and IL-1 β and TNF- α in synovial fibroblasts [89]. IL-1 β and TNF- α upregulate LIF production [18,36,56]. LIF regulates the metabolism of connective tissue such as cartilage and bone [1,69], induces expression of collagenase and stromelysin but not tissue inhibitor of metalloproteases, TIMP [56]. This cytokine stimulates cartilage proteoglycan resorption [20] as well as nitric oxide (NO) production.

The IL-11 receptor shares the gp 130 domain with the LIF and IL-6 receptors, suggesting that they may have similar actions. This cytokine was originally identified as a stromal cell-derived lymphoietic and hematopoietic factor, but can also be induced in articular chondrocyte and synovial fibroblast cultures [58,65]. IL-11 has been found to decrease the release of PGE₂ from OA synovial fibroblasts [6], suggesting that IL-11 can prevent the excessive extracellular matrix degeneration induced by synovial inflammation.

IL-17 is a newly discovered cytokine of 20–30 kD present as a homodimer with variable glycosylated polypeptides [92]. The tissue distribution of IL-17R appears ubiquitous, and it is not yet known whether all cells expressing IL-17R respond to its ligand. IL-17 upregulates a number of gene products involved in cell activation, including the proinflammatory cytokines IL-1 β , TNF- α and IL-6, as well as MMP in target cells such as human macrophages [46]. IL-17 also increases the production of NO in chondrocyte cultures [9,60].

2.2. Antiinflammatory cytokines

Three antiinflammatory cytokines (IL-4, IL-10, and IL-13) are spontaneously elaborated by synovial membrane and cartilage, and are found in increased levels in the synovial fluid of OA patients. The antiinflammatory properties of these cytokines include decreased production of IL-1beta, TNF-alpha and MMP, upregulation of IL-1Ra and TIMP-1, and inhibition of PGE₂ release [5,30,31,38,39,47,78,88]. It was found that IL-10 modulated TNF-alpha production by increasing the release of the TNF-sR from monocytes in culture, while downregulating the receptor surface expression [38]. In human OA synovial fibroblasts, IL-10 also downregulated the TNF-R density, while increasing the release of TNF-alpha-induced TNF-Rs75. In these cells, however, IL-4 upregulated TNF-R, and enhanced TNF-alpha-induced TNF-sR75 [5]. In mononuclear cells from RA synovial fluid, both TNF-R55 and TNF-R75 are upregulated by IL-4 [23], and contrasts with data from monocytes, where this antiinflammatory cytokine downregulated both the membrane and soluble TNF-R [48].

IL-13 has been shown to have important biological activities such as inhibiting the production of a wide range of proinflammatory cytokines, while increasing IL-1Ra production [24,26]. In human synovial membrane specimens from OA patients treated with LPS, *in vitro* IL-13 inhibited the synthesis of IL-1beta, TNF-alpha and stromelysin, and increased production of IL-1Ra [47], but not in cells recovered from the synovial fluid of OA and RA patients [24]. The TNF receptor system does not appear to be a target for IL-13 in OA synovial fibroblasts [5].

IL-1Ra is a competitive inhibitor of IL-1R. This molecule does not bind to IL-1, is not a binding protein, nor does it stimulate target cells. IL-1Ra can block many of the effects observed during the pathological process of OA, including PGE₂ synthesis in synovial cells, collagenase production by chondrocytes, and cartilage matrix degradation. Three forms of IL-1Ra were found, one extracellular and termed soluble IL-1Ra (IL-1sRa), and two intracellular, icIL-1RaI and icIL-1RaII [8]. Both the soluble and icIL-1Ra can bind to IL-1R, but with about 5-fold less affinity for the latter. Although intensive research is underway, the biological actions of icIL-1Ra remain elusive. *In vitro* experiments have revealed that an excess of 10–100 times the amount of IL-1Ra is necessary to inhibit IL-1beta activity whereas, *in vivo*, 100–2000 times more IL-1Ra is needed [8,67]. This may likely explain why, even though a higher level of IL-1Ra is found in OA articular tissue, there is a relative deficit of IL-1Ra to IL-1beta in this tissue. This in turn may cause the increased level of IL-1beta activity.

3. Potential therapeutic applications of cytokine modulation in OA

The neutralization of IL-1 and/or TNF- α up-regulation of MMP gene expression appears to be a logical development in the potential medical therapy of OA. Indeed, recombinant IL-1 receptor antagonists (ILRa) and soluble IL-1 receptor proteins have been tested in both animal models of OA for modification of OA progression. Soluble IL-1Ra suppressed MMP-3 transcription in the rabbit synovial cell line HIG-82. Experimental evidence showing that neutralizing TNF- α suppressed cartilage degradation in arthritis also supports such strategy. The important role of TNF- α in OA may emerge from the fact that human articular chondrocytes from OA cartilage expressed a significantly higher number of the p55 TNF-alpha receptor that could make OA cartilage particularly susceptible to TNF-alpha degradative stimuli. In addition, OA cartilage produces more TNF- α and TNF- α convertase enzyme (TACE) mRNA than normal cartilage. By analogy, an inhibitor to the p55 TNF- α receptor may also provide a mechanism for abolishing TNF- α -induced degradation of cartilage ECM by MMPs. Since TACE is

the regulator of TNF- α activity, limiting the activity of TACE might also prove efficacious in OA. IL-1 and TNF- α inhibition of chondrocyte compensatory biosynthesis pathways which further compromise cartilage repair must also be dealt with, perhaps by employing stimulatory agents such as transforming growth factor-beta or insulin-like growth factor-I.

The capacity of IL-1Ra to reduce *in vitro* and *in vivo* cartilage degradation, MMP production and the progression of OA lesions [19,66] has elicited much attention concerning the use of this molecule in OA therapy, and more particularly in regard to gene therapy. Using the MFG retrovirus, the IL-1Ra gene has been successfully transferred into animal and human synovial cells using an *ex vivo* technique [10,32]. One such study using the experimental dog model of OA showed *in vivo* that the progression of structural changes of OA was significantly reduced [66]. It has also been demonstrated *in vitro* that the human IL-1Ra gene can be successfully transferred into chondrocytes using the Ad.RSV adenovirus, and that the resulting increase in production of IL-1Ra can protect the OA cartilage explants from degradation induced by IL-1 [10].

A novel and interesting approach to controlling proinflammatory cytokine production and/or activity is the use of biological molecules possessing antiinflammatory properties. Augmenting inhibitor production *in situ* by gene therapy or supplementing it by injecting the recombinant protein is an attractive therapeutic target, although an *in vivo* assay in OA is not available, and its applicability has yet to be proven. As such, recombinant human IL-4 (rhIL-4) has been tested *in vitro* on OA synovial tissue, and has been shown to suppress the synthesis of both IL-1beta and TNF-alpha in the same manner as low-dose dexamethasone [11]. To date, of the antiinflammatory cytokines, only IL-10 is employed in clinical trials for the treatment of RA in humans. Results from IL-13 experimentation on human synovial membrane from OA patients [47] indicate it is potentially useful in the treatment of this disease.

4. Conclusion

Although the primary etiology of OA remains undetermined, it is now believed that cartilage integrity is maintained by a balance obtained from cytokine-driven anabolic and catabolic processes. In OA, the specific causative for the pathological process has not been identified, but synovial inflammation at the clinical stage is now a well-documented phenomenon. An excess of proinflammatory cytokines is thought to be responsible for many clinical manifestations of OA. Other cytokines having anti-inflammatory properties could modulate this pathological process; therefore, these cytokines may prevent inflammation in OA.

In summary, modulation of cytokines that control MMP gene up-regulation would appear to be fertile targets for drug development in the treatment of OA. Several studies illustrate the potential importance of modulating IL-1 activity as a means to reduce the progression of the structural changes in OA. In the experimental dog and rabbit models of OA, we have demonstrated that *in vivo* intraarticular injections of the IL-Ra gene can prevent the progression of structural changes in OA. Future directions in the research and treatment of osteoarthritis (OA) will be based on the emerging picture of pathophysiological events that modulate the initiation and progression of OA.

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